REMARKS

On page 2 of the Office Action, the Examiner rejects Claims 10-18 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner rejects the claims because they encompass "prevention" of disease.

In view of the amendments to the claims, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

On page 4 of the Office Action, the Examiner rejects Claims 10-18 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner objects to the phrase "psoriasis with skin affection", as it is unclear what type of psoriasis is being referred to, and what type of psoriasis is not encompassed by the phrase.

In view of the amendments to the claims, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

On page 5 of the Office Action, the Examiner rejects Claims 10-18 under 35 U.S.C. § 103 as being obvious over Olsen et al.

Specifically, the Examiner states that Olsen et al discloses that psoriasis in a mammal can be treated by administering to the mammal chondroitin sulfate, which can be obtained from animal cartilage.

The Examiner notes that Olsen et al does not teach the use of an alkaline earth metal chondroitin sulfate, as claimed. However, the Examiner states that Olsen et al suggests that pharmaceutically acceptable salts, which would include an

alkaline or alkaline earth metal salt, can be used (see page 18, lines 16-21 thereof). Hence, the Examiner contends that it would have been obvious in view of Olsen et al to administer a pharmaceutically acceptable salt of chondroitin sulfate, such as sodium chondroitin sulfate, to treat psoriasis in a mammal.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Olsen et al relates to a method of producing anti-angiogenic, anti-inflammatoric, lysozomic and/or anti-collagenolytic fractions and/or collagen and/or chondroitin sulfate from *in vitro* cultured chondrocytes. Olsen et al also relates to the use of said anti-angiogenic, anti-inflammatoric, lysozomic and/or anti-collagenolytic fractions and/or collagen and/or chondroitin sulfate obtainable from *in vitro* culturing of chondrocytes for cancer, psoriasis, lupus, immunological disease, diabetes related disease, or inflammatoric joints related disease.

Olsen et al does not teach or suggest the use of chondroitin sulfate directly obtained from animal cartilage to treat psoriasis.

In addition, Olsen et al does not describe a method of directly producing chondroitin sulfate from animal cartilage. Rather, Olsen et al teaches a method of producing chondrocytes from animal cartilage. Olsen et al may suggest obtaining chondroitin sulfate from said cultured chondrocytes, but does not describe a method for doing so. Olsen et al claim that chondroitin sulfate obtained from *in vitro* chondrocytes is a new product due to the "product-by-process" claim (see Claim 29 of Olsen et al). However, in Olsen et al, it is not disclosed how

to extract said chondroitin sulfate. It is only said that "Chondroitin sulfate and collagen may be obtained from the cell cultures using either physical or chemical separation and purification techniques" (see page 15, lines 31-32, of Olsen et al).

There is nothing in Olsen et al about the characteristics of the chondroitin sulfate obtained from said cultured chondrocytes, nor is there any scientific data which demonstrate the beneficial effect of the chondroitin sulfate obtained from the *in vitro* cultured chondrocytes for treating psoriasis, or for any of the other diseases mentioned in Olsen et al. Olsen et al does not disclose any study with Psoriatic Patients treated with chondroitin sulfate. Olsen et al does not disclose any clinical activity of chondroitin sulfate. Olsen et al only discloses a way to obtain anti-angiogenic fractions (see Example 2 of Olsen et al) and the activity of said fractions in an *in vitro* assay with cancer cell lines (see Example 3, page 30, lines 1-10, of Olsen et al). An *in vivo* assay with rats that had developed a breast cancer is also disclosed (see Example 3, page 30, lines 11-22, of Olsen et al).

The Examiner is requested to note that chondroitin sulfate obtained from cultured chondrocytes, as taught in Olsen et al, is different from chondroitin sulfate obtained from enzymatic hydrolysis of animal cartilage. It is known (Morrison et al, U.S. Patent 3,895,106) that differences in the activity of different preparations of purified chondroitin sulfates are both due to the differences in the method of preparation and the use of different starting materials. It is also known that chondroitin sulfates obtained from enzymatic hydrolysis of

animal cartilage show differences in physical and chemical assays, depending on the techniques of extraction or purification (Barnhill et al, *J.A.P.H.A.*, 46(1):14-24 (2006); a copy of which is attached hereto), and also show differences in the permeability through the gastrointestinal tract, that could lead to differences in bioavailability (Adebowale et al, *JANA*, 3(1):37-44 (2000); a copy of which is attached hereto). Said differences in chondroitin sulfates lead to different effects for the treatment of psoriasis.

Furthermore, Olsen et al does not provide any suggestion that can lead a skilled person to use chondroitin sulfate obtained directly by an enzymatic hydrolysis of animal cartilage for the treatment of psoriasis. In fact, Olsen et al teaches away from directly using cartilage by stating that it is important that the chondrocytes are at least partly denuded before culturing from the extracellular matrix, in order to obtain purer fractions compared to fractions obtained directly from cartilage (see page 10, lines 16-22, of Olsen et al). Olsen et al base their method on chondrocytes and recommend not working directly with the cartilage (see page 7, lines 24-31, of Olsen et al). Therefore, the issue is not whether a skilled person could have arrived at the present invention by modifying the prior art (Olsen et al), but whether one would have done so, taking into account the teaching of Olsen et al.

Moreover, a skilled person in the art (an expert in the field of cellular cultures, as well as in the field of glycosaminglycans) knows that obtaining chondroitin sulfate by means of *in vitro* cultured chondrocytes would be non-viable from an industrial and economic point of view, due to the large

amount of colonies of chondrocytes that would be required to isolate a small amount of chondroitin sulfate for use in the treatment of psoriasis. For example, in an industrial biotechnology reactor of 20,000 L, only 11g of chondroitin sulfate would be isolated. In order to calculate the amount of chondroitin sulfate that could be isolated, the following documents have been taken into account:

1. In 100 g of Proteoglycans (PG), there are 20 g of chondroitin sulfate (Jollés, *Proteoglycans*, 70:145-177 (1994); a copy of which is attached hereto);
2. Relation between Proteoglycans and DNA: 200 ng PG/µg of DNA (Condroitin sulphate: structure, role and pharmacological activity, Volpi, *Advances in Pharmacology*. 53:449-465 (2006); a copy of which is attached hereto);
3. Relation between mammals cells (for example chondrocytes) and DNA: 6 pg of DNA/cell (Lehninger, "The molecular basis of cell structure and function", Worth Publishers, Inc., New York, third printing, *Biochemistry* (1971); a copy of which is attached hereto);
4. In 1 cm^3, there are $2.3x10^6$ cells (Freiría et al, "Influence of medium composition, static and stirred conditions on the proliferation of and matrix protein expression of bovine articular chondrocytes cultured in a 3-D collagen scaffold" *Biomaterials*, 25(4):687-697 (2004); a copy of which is attached hereto). Olsen et al worked

with concentrations lower than $1x10^6$ cells/mL, which corresponds to concentrations lower than 10^3 cells/cm^3 (see Olsen et al, page 26, line 23), which means that they would obtain even a smaller amount of chondroitin sulfate; and

5. A reactor used in biotechnology with a capacity of 20,000 L has been taken into account to make the calculation.

Taking into account that in a two-month standard clinical treatment, a psoriatic patient is administered 48g of chondroitin sulfate (see Example 2 of the present application), it is not possible to isolate enough chondroitin sulfate by means of cultured chondrocytes for the treatment of a unique psoriatic patient. On the other hand, in an industrial biotechnology reactor of 20,000 L and by means of an enzymatic hydrolysis of cartilage, 350 kg of chondroitin sulfate already purified can be obtained.

Hence, a skilled person in the art after reading Olsen et al would not be motivated to look for another chondroitin sulfate, specifically for chondroitin sulfate obtained directly from hydrolysis of animal cartilage, nor use the same to treat psoriasis.

The Examiner is requested to note that sodium chondroitin sulfate, which has an average molecular weight of between 10,000 and 40,000 daltons (Claim 13); and sodium chondroitin sulfate, which has an average molecular weight of between 10,000 and 20,000 daltons (Claim 14), are isolated from either bovine cartilage or pig cartilage. The preferred chondrocyte source in Olsen et al is elasmobranch cartilage (see Claim 3; page 7,

line 6; and page 8, lines 11-12, of Olsen et al); and more specifically ray or shark chondrocytes (see Claim 5 of Olsen et al). The chondroitin sulfate obtained from ray or shark cartilage has an average molecular weight greater than 50,000 daltons (see for example Volpi, "Analytical Aspects of Pharmaceutical Grade Chondroitin Sulphates", *J. Pharm Sci.*, 96:3168-3180 (2007); a copy of which is attached hereto).

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Olsen et al, and thus request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the below-listed number on any questions which might arise.

Respectfully submitted,

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